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| 08/993,564 | 12/18/1997 | STUART A. NEWMAN | 45010-00601 | 5286 |

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EXAMINER

CROUCH, DEBORAH

| ART UNIT | PAPER NUMBER |
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1632

28

DATE MAILED: 10/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

08/993,564

Applicant(s)

NEWMAN, STUART A.

Examiner

Deborah Crouch

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 05 June 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,3,4,6,7,10,28,30,31,33,34,59,72,73,75-77 and 91-106 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,3,4,6,7,10,28,30,31,33,34,59,72,73,75-77 and 91-106 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

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Applicant's arguments filed April 29, 2003 and June 5, 2003 have been fully considered but they are not persuasive. The amendment has been entered. Claims 1, 3, 4, 6, 7, 10, 28, 30, 31, 33, 34, 59, 72, 73, 75-77 and 91-106 are pending.

The rejection of claims 13, 50, 66-71, 83 and 86-90 under 35 U.S.C. 102 in the office action mailed January 29, 2003 has been withdrawn as these claims have been canceled. The rejection of claims 38-43, 60-65, 74, 79, 81 and 82 under 35 U.S.C. 103 in the office action mailed January 29, 2003 has been withdrawn as these claims have been canceled.

The rejection of claims 1, 28, 33, 34, 59, 72, 73, 75, 76, 91, and 92 in the office action mailed January 29, 2003 under 35 U.S.C. 103 over Gustafson et al (1993) has been withdrawn. Applicant is correct in the assertion that Gustafson does not disclose chimeric embryos. The examiner agrees that the embryos of Gustafson were prepared by in vitro fertilization and thus the embryos cannot be comprised of cells of different species as presently claimed.

The rejection of claims 13, 38-43, 50, 53, 55, 60-71, 74 and 78-90 under 35 U.S.C. 112, first paragraph as lacking written description and for lacking an enabling disclosure in the office action mailed January 29, 2003 has been withdrawn due to applicant's cancellation of these claims.

The rejection of claims 1, 3, 4, 6, 7, 10, 28, 30, 31, 33, 34, 59, 72, 73, 75-77, 91 and 92 under 35 U.S.C. 112, second paragraph in the office action mailed January 29, 2003 has been withdrawn because of applicant's arguments.

The rejection of claims 13, 38-43, 50, 53, 55, 60-71, 74 and 78-90 under 35 U.S.C. 112, second paragraph in the office action mailed January 29, 2003 has been withdrawn because applicant canceled these claims.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent

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the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 3, 4, 6, 7, 28, 30, 31, 33, 34, 59, 72, 73, 75-77 and 91-106 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 37-50 of copending Application No. 10/308,135. Although the conflicting claims are not identical, they are not patentably distinct from each other because the presently claimed embryos are used to produce the chimeric animals of claims 37-50 of '135. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not is patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

Present claims 1, 3, 4, 6, 7, 28, 30, 31, 33, 34, 59, 72, 73, 75-77 and 91-106 are drawn to chimeric embryos comprising human and nonhuman primate cells. Claims 37-50 of '135 are drawn to chimeric animals that have developed from a chimeric embryo comprising human and nonhuman primate cells. An obvious use of the presently claimed chimeric embryos is to produce chimeric animals, as stated in the claims of '135. Thus, at the time of the present invention, it would have been

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obvious to the ordinary artisan to make and use the presently claimed chimeric embryos to produce chimeric animals given claims 37-50 of '135.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 10 stands rejected under 35 U.S.C. 102(b) as being anticipated by ATCC entries HTB 157, 158, and 160 for reasons set forth in the office action mailed cells for reasoning set forth in the office action mailed January 29, 2003. It is noted that ATCC entries HTB 157, 158 and 160 are isolated human embryonic and fetal cell lines.

Claim 10 stands rejected under 35 U.S.C. 102(b) as being anticipated by ATCC entry CRL-2378, designated MA-104 cells for reasoning set forth in the office action mailed January 29, 2003. It is noted that ATCC entry CRL-2378 is a Rhesus monkey embryonic kidney cell line.

It is noted that applicant did not respond to the rejection of claims 10, 50 and 68 under 35 U.S.C. 102(b) as being anticipated by ATCC entry CRL-2378. However, the examiner will assume that applicant intended the same argument for this rejection as for the argument presented for rejection of claims 10 and 68 under 35 U.S.C. 102(b).

Applicant argues that claim 10 has been amended to state that the cell line is "tolerated by said first and second animal species" where the first animal species is

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human and the second animal species is nonhuman primate. Applicant argues that as described in the specification (page 10, lines 14–20), immune tolerance is measured by a mixed lymphocyte response. Applicant argues that in order to anticipate claim 10, the cell lines cited in the rejection would need to be tolerated by both human and nonhuman primates. Applicant argues that since the cited cells are human embryonic cells or human fetal cells, the cell lines would not be tolerated in a nonhuman primate. These arguments are not persuasive.

A first issue is clarification of applicant's specification citation. It appears that applicant meant page 11, lines 14-20, not page 10, lines 14-20. The examiner could not locate, at applicant's citation, the particular disclosure discussed. The citation at page 11, discloses Gustafson (1993) who teaches that some sheep and goat siblings of geeps tolerated skin grafts from the chimeras and the siblings demonstrated immune tolerance to the chimeric siblings in a mixed lymphocyte response. However, this does not provide evidence that a cell from any of the cell lines cited in the rejection would not be "tolerated" by both human and nonhuman primate species. The examiner would like to point out that the claim is to a cell line that is comprised of individual cells. Any one cell of the cell line would be either human or nonhuman primate. The method of producing chimeras does not allow for the mixing of genomes. Thus, no one cell would have both human-nonhuman primate proteins to induce tolerance in both species.

Humans and Old World Primates, such as the baboon, are taught by the art at the time of filing as being closely related immunologically. That is, they would not exhibit hyperacute rejection as seen in the rejection of tissues of human-pig or human-ape or Old World Primate transplantation. In this regard human-baboon transplantation is referred to as concordant. (See Lambrigts, page 547, col. 2, parag. 2). Thus, there would be a reasonable expectation of success for either a human cell

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or nonhuman Old World primate cell line to be tolerant by both the human and nonhuman primate species that make up the chimeric embryo. Further, Starzl discloses baboon and chimpanzee organs were tolerated for some period of time when transplanted into a human, which provides for a reasonable expectation of success. If a baboon or chimpanzee organ can be immunologically tolerated by a human species, then a cell from a human would also be immunologically tolerated in a baboon or chimpanzee. This evidence, and description in the art at the time of filing, provides that either humans or nonhuman primates would inherently immunologically tolerate the human cell lines cited.

"Immunologically tolerated" can be defined by more than just a mixed lymphocyte assay, which incidentally, is not a limitation of the claim. Tolerance can be measured by observation, as in the baboon or chimpanzee organ transplantations of Starzl. Additionally, the specification provides no definition of "immunologically tolerated". Based on the lack of definition, one could reasonably decide, for example, that if a cell was not rejected for an hour after implantation, then that the cell was immunologically tolerated by the host species. Without a definition of "immunologically tolerated" any cell line that doesn't undergo hyperacute rejection when implanted would fall within the scope of the claim. Therefore, the art provides sufficient evidence to support the conclusion that the human cell lines of the prior art would be "immunologically tolerated" by both human and nonhuman primate species for some measurable period of time. Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product (*In re Ludtke*). Whether the rejection is based on "inherency" under 35 USC 102, on "prima facie obviousness" under 35 USC 103, jointly or alternatively,

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the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. *In re Best, Bolton, and Shaw*, 195 USPQ 430, 433 (CCPA 1977) citing *In re Brown*, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972). Applicant has not provided any evidence to support their argument that the cited cell lines would not be immunologically tolerated by human and nonhuman primate species.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 4, 6, 7, 28, 30, 31, 33, 34, 59, 72, 73, 75-77, 91 and 92 remain and newly added claims 93-106 are rejected under 35 U.S.C. 112, first paragraph, as failing to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. The rejection is maintained for the reasons set forth in the office action mailed January 29, 2003.

Applicant argues that the skilled artisan can envision the detailed structure of the claimed chimeric embryo. Applicant argues that the term "chimeric embryo" as used in the present specification is in the same manner as the term's use in the art. Applicant argues that the chimeric embryo contains cells derived from two animal species, such as the presently claimed human/nonhuman chimeric embryos. Applicant provides several definitions of "chimeric embryo," each of which state that the chimeric embryo is composed of blastomeres or ES cells from early stage embryos of more than one species, or the combination of early cleavage stage embryos from more than one species of animal. Thus, applicant argues the skilled artisan can envision that the chimeric embryo of the claims contains cells from both human and human primate species. These arguments are not persuasive.

The term "embryo" covers a very broad range of developmental states from two cells, a requirement in this application, to a multicellular embryo that has begun organogenesis. Thus, there is no description with sufficient relevant identifying characteristics of the invention as a whole such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. It is maintained that the skilled artisan cannot envision the detailed structure of the claimed chimeric embryos with respect to human/non-human primate cellular contribution of the final product embryo, and thus, for these inventions, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. One cannot describe what one has not conceived. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993).

Claims 1, 3, 4, 6, 7, 28, 30, 31, 33, 34, 50, 53, 55, 59, 72, 73, 75-77, 19, 92 and 92 stand, and newly added claims 93-106 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The rejection is maintained for the reasons set forth in the previous office action mailed January 29, 2003.

The enablement rejection, in summary, is that the specification fails to provide sufficient guidance to make and use human/nonhuman primate chimeras. Neither the art at the time of filing nor the present specification provide the requisite guidance as to the methodology that would lead to the production of these chimeras without an undue amount of experimentation without a predictable degree of success.

Applicant cites many references in support of their allegation that the claims are enabled as the art at the time of filing was replete with techniques for

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mammalian embryo manipulations. However, none of the references cited by applicant have been supplied to the examiner for review. Without the references, the examiner is unable to give a complete analysis but will comment to the extent possible given applicant's excerpts from these references.

Applicant argues that techniques for manipulating mammalian embryos were robust and known in the art at the time of filing. Applicant cites Hammer (1998) as providing evidence that a foundation of the biology of early mammalian eggs was established between 1960 and 1970. Applicant argues that novel approaches to cell sampling from preimplantation ovine embryos and its use in embryonic genome analysis (Leoni, 2000) also speaks to the robustness of mammalian embryo manipulation techniques, especially as useful for reproductive technologies of domestic, wild and human species. These arguments are not persuasive.

Both Hammer and Leoni are discussing methods of manipulation of embryos that are derived from the same species. The best that the examiner can deduce, is that Hammer is discussing the importance of egg culture techniques in the production of transgenic mice, and that Leoni is discussing a method to analyze cells of an embryo produced from in vitro fertilization. In Leoni, the method would be applicable to analyze cells of a human/nonhuman primate chimeric embryo, but it does not teach how to produce a viable chimeric embryo. It is the absence of such teachings that is the thrust of the enablement rejection over applicant's claims to human/nonhuman chimeric embryos.

Applicant argues that Anderson (1985) teaches that by the early 1980's the robustness of mammalian embryo manipulation techniques and their transferability across species lines was already part of the practice in the field. Anderson is quoted as stating "the mammalian embryo possess the unique capacity to regulate its development and differentiate into a normal individual after being stimulated to

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incorporate foreign cells or after a production of its cells are removed." Anderson also states that this ability is useful in the production of chimeras. Applicant then cites Picard (1990) for the production of chimeric bovine embryos; Onishi (1994) for the production of chimeric pigs and analysis using mitochondrial DNA as a marker; Schoonjans (1996) for the formation of coat color chimeras in rabbits; Sumantri (1997) for the fertility of sperm from a tetraparental chimeric bull. These arguments are not persuasive.

These chimeras were same species chimeras and not of different species chimeras, which is the subject matter of the claims. The examiner would agree that same species chimeras were known at the time of filing, same species chimeras meaning mouse/mouse; bovine/bovine; pig/pig, and the like. However, the claims are not to same species chimeric embryos but interspecies chimeric embryos. An embryo that comprises both human and nonhuman primate embryos is not of the same species. The formation of fertile sperm in the tetraparental chimeric bull (Sumantri) only indicates that the bull's germ cells were competent although the cells themselves may have been derived from any one or any combination of the four parents. There is no indication that the bull comprises another species cells such as human, sheep or rabbit. The manipulation of any type of chimeric embryo is not the subject of the claims and thus not addressed in the rejection.

Applicant argues that there is evidence of intrauterine chimerism in humans (De la Chapelle (1974); and Mayr (1979)). This argument is not persuasive.

Again, the formation of human chimeras, which the examiner agrees is well known, is same species chimerism. There is no evidence in applicant's statement that the chimerism involving humans is between a human embryonic cell and any other species of embryonic cell. A full review of these references, however, is not possible as applicant has not submitted them.

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Applicant argues that the examiner stated that none of the prior art methods enable the ordinary artisan to culture primate embryos. This argument is not persuasive.

The statements by the examiner were directed to explaining why the art at the time of filing did not teach a methodology for the culture of human/nonhuman primate embryos. The comments made in the office action mailed January 29, 2003 state:

Applicant cites references to support that primate embryos may be cultured. See page 32 of the Amendment and Response). However, none of these references provide a nexus between primate embryos and a human/non-human primate embryo. The ability to culture a primate embryo cannot be extrapolated to the ability to make and use a cross-species human/primate chimeric embryo.

As is clearly obvious from this quote, the examiner is stating that there is no nexus between the methods of culture for primate embryos and methods of culture of human/nonhuman primate embryos. Further each of the references cited by applicant to support their argument is directed to same species primate embryo culturing (Pope (1982); Gould (1983); Pope (1984); Fourie (1987); and Pope (1997). Applicant further cites Homa (1994); Herbert (1995); Prather (1996); Prather (1991); Chan (2000); Bavister; Boatman; Leibfried (1983); Boatman (1987); Lanzendorf; Zelinski-Wooten; and Stouffer (1990.) These references also are apparently directed to the culture of nonchimeric embryos. The examiner would agree that at the time of filing methods were known for the culture of nonchimeric primate embryos. However, only Bavister (1983) and Boatman (2987), Chan, Prather (1991), Prather (1996), Machaty and Yanagimachi are of record. None of these references, as stated in the previous office action, disclose the formation of

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embryos by the aggregation of human/nonhuman primate embryonic cell types as is required for the present claims.

Applicant argues that all mammalian embryos, including human embryos, undergo the same initial development steps. Applicant provides a discussion of the embryonic stages and embryonic cells that are common features among mammalian embryos. Applicant then argues that methods to create chimeric embryos were adequately disclosed and enabled in the present invention.

It is reiterated that the claims are not to same species chimeric embryos. The claims are to human/nonhuman primate embryos. None of the references that applicant has cited, and none found by the examiner, address the culture of human/nonhuman primate embryos. The issue isn't that the skilled artisan at the time of filing could not have produced same species chimeric embryos, but that at the time of filing, the art and the specification did not teach how to produce and culture nonhuman/primate embryos. Further, applicant has stated the stages common to mammalian embryos, but applicant has not drawn a conclusion as to why this commonality would enable the production of human/nonhuman primate embryos. Just because mammalian embryos go through common developmental stages does not mean that the media, media components, serum and the like, for the culture of any one mammalian embryo will be useful in the culture of a different species mammalian embryo or a human/nonhuman chimeric embryo.

Applicant summarizes the examiner's statements made in the office action mailed January 29, 2003, regarding sequence homology between chimp and human and not accounting for anatomical differences, differences in gestation and differences in getting pregnancy to develop in a host female. Applicant offers no argument as to why the examiner's argument is flawed. Applicant only repeats that

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applicant believes that the art at the time of filing was sufficient to guide the ordinary artisan to implement the claimed invention.

Applicant argues that the present specification is enabling for human/nonhuman primate chimeras but also for human/animal chimeras. Applicant provides two references: DeWitt (2003) and Check (2003). Applicant argues that these references indicate that techniques, such as those disclosed in the present application, will be used to create these chimeras. These arguments are not persuasive.

DeWitt does not support applicant's allegations of enablement because DeWitt is a report of a meeting held in November 2003. While researchers at this meeting were discussing injecting human ES cells into mouse embryos, there is no evidence that such methodology was ever conducted, much less any description of the developmental ability of the chimeric embryos. Further, Rossant, an attendee of the meeting, is quoted as saying "for one thing, ..., the different gestation periods for mice and humans make it unlikely that the cells will combine in the embryo" (Check, col. 2-3, bridg. sent.). Thus, clearly one of skill in the art has reason to question the ability to make a chimeric mouse/human embryo without undue experimentation. The quotation also bolsters the enablement rejection, which states that differences in gestation periods would render success in making the claimed invention unpredictable. Applicant is also reminded that the present claims are to human/nonhuman primate embryos, and the present claims no longer include mouse/human embryos. The discussion in DeWitt is not of the same scope as the claims, and thus does not, even in a general sense of what the art wants to try, support the enablement of the claimed invention. Check doesn't provide support for applicant's arguments of enablement. Check is a summary of the present inventors' interactions with other skilled artisans. There is no discussion or description of any

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methods that maybe used to make and use the claimed human/nonhuman primate chimeras.

Applicant argues that the present claims are to a chimeric embryo comprising both human and nonhuman primate embryonic cells that remain attached to one another and which cooperate in the formation of a developing embryo. Applicant argues that the specification fully enables the production of such embryos. Applicant argues that the specification fully enables the use of the embryos by the examiner's conclusion that the chimeric embryos have utility for (1) development toxicology assays, (2) studies of embryonic development disorders, (3) cryopreservation for future use. These arguments are not persuasive.

Uses 1-3, as discussed by applicant, were not stated in the Office action mailed January 29, 2003 as being enabled. Applicant's citation of page 30 puts these examiner's statements in the rejection of the claims under 35 U.S.C. 101 as lacking a specific or substantial utility. If claims lack utility under 101, then those claims are also not enabled. The specification in this regard provides no guidance on how to use completely artificial embryos, that is ones that are not known to exist in the wild, in any of the three uses argued. There is no guidance as to the application of any information gleaned from any of these uses in the areas of embryonic development, much less cryopreservation for future use.

Applicant argues that the specification is enabling for the use of human ES cells and maintains that undue experimentation would not have been required to produce human ES cells. Applicant argues that nonhuman ES cells have been documented in the art at the time of filing. Applicant cites Martin (1981) ; Wheeler (1994) ; Thomson (1995) and Thomson (1996). Applicant argues that mouse embryonic stems cell were established from preimplantation mouse embryos, from the inner cell mass, and that these cells were pluripotent. Applicant argues that

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embryonic stem cells that developed into several different tissue types have been prepared from marmoset blastocyst. Applicant also argues that post-filing human ES cells were made. Applicant cites Thomson (1998), Shambloott (1998), Bongso (1994) and Moreadith (1997). Applicant argues that human ES cells did not require undue experimentation. These arguments are not persuasive.

The fact that ES cells of animal species, both nonhuman primate and human, were known at the time of filing (nonhuman primate) or shortly after filing (human) is not relevant to the rejection of record. The unpredictability lies in the production of a chimeric embryo. There is no evidence that a chimeric human/nonhuman primate embryo, as claimed, could be produced by the insertion of a nonhuman primate ES cell into a human embryo, or by the insertion of a human ES cell into a nonhuman primate embryo. The examiner has mentioned that differences in gestation periods would be a factor in the unpredictability, and this factor has been support by the art. As stated above, Check quotes researcher Rossant as saying "for one thing, ..., the different gestation periods for mice and humans make it unlikely that the cells will combine in the embryo" (Check, col. 2-3, bridg. sent.). Further, the claims are to an "embryo." "Embryo" is broad term, which in the context of the claimed invention encompasses a two-celled embryo through a blastocyst and up to point where the embryo becomes a fetus, at about eight weeks after conception (see, e.g., Stedman's Medical Dictionary, 26th ed., 1995). Thus applicant's invention would need to predictably enable the production of a chimeric human/nonhuman primate embryo through all embryonic stages. Given the statements of Rossant, it appears unlikely that the claimed chimeric embryos, throughout their various developmental stages, could be made without undue experimentation.

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Claims 1, 3, 4, 6, 7, 28, 30, 31, 33, 34, 59, 72, 73, 75-77, and 91-106 stand rejected under 35 USC 101 as being directed to non-statutory subject matter for reasons of record.

Applicant argues that the claims (1) do not encompass a human being or human embryo by their plain language, and (2) are directed to subject matter made by man. Applicant also argues that the statute does not authorize rejecting claims on the grounds that they are directed to a human being. These arguments are not persuasive.

The claims include a chimeric embryo comprising human and non-human primate cells. The claims use broad terms without defining any distinction between human and non-human embryos. The broadest reasonable interpretation of the claims is that human and non-human embryos are included.

Medical literature shows that a human being may comprise a proportion of non-human cells. For example, Starzl et al., of record, reported on treatment of patients with cells engrafted from a primate. The addition of a proportion of baboon or chimpanzee cells to the human patient did not convert the human patient to a non-human. Thus, Applicant's general argument that embryos not exclusively human in origin are not human is unpersuasive. Applicant also argues that a proportion of human cells in a chimeric embryo does not make the embryo human, drawing an analogy to an example of a proportion of human cells added to a mouse fetus (as reported in Pixley et al). However, the claims are broadly drawn and cover an embryo with any minor or major proportion of human cells. The claims are thus reasonably read to include human embryos.

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Applicant argues that the statute does not restrict patentability for claims covering a human being, and that any invention made by man is eligible for patenting. When interpreting statutory language, words of a statute are given their ordinary, contemporary, common meaning. The prior Office actions set out the reasoning for considering that a human being at any stage of development is not patent eligible subject matter. For the reasons already stated in the record, the USPTO prefers to defer to Congress the task of expanding the statute. When recently construing 35 U.S.C. § 271(g), the Federal Circuit made the following comments: "In the face of silence in the legislative history, here as to the coverage beyond manufactured articles, courts are reluctant to broadly interpret the legislation. See *Dewsnup v. Timm*, 502 U.S. 410, 419 (1992) (stating that "th[e] Court has been reluctant to accept arguments that would interpret the [Bankruptcy] Code, however vague the particular language under consideration might be, to effect a major change in pre-Code practice that is not the subject of at least some discussion in the legislative history"). . . .

The legislative history's very silence thus suggests that Congress did not intend to expand coverage beyond manufactured articles. . . . Under these circumstances we think it best to leave to Congress the task of expanding the statute if we are wrong in our interpretation." *Bayer AG v. Housey Pharm., Inc.*, 2003 WL 21991600 *7-8 (Fed. Cir. Aug. 22, 2003).

Claims 1, 3, 4, 6, 7, 10, 28, 30, 31, 33, 34, 59, 72, 73, 75-77, and 91-106 stand rejected under 35 USC 101 as lacking patentable utility for reasons of record.

Applicant argues that the utilities proposed in the specification are specific and substantial. Rather than discuss all the proposals in the specification, Applicant limits the response to a discussion of two utilities: toxicology assays and

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development studies. According to Applicant, the proposed toxicology assays and studies of embryonic development disorders are real world uses that meet the requirement for a specific and substantial utility.

The arguments are not persuasive. Even assuming toxicology studies are a critical step in the development of new drugs, the specification's proposal for toxicology studies is so general as to be meaningless. Similarly, there is no specific explanation showing that observing the development of the claimed chimeras would have any practical utility. The proposed utilities appear to be the kind of "use testing" that does not meet the statutory requirement. That is, the claimed invention has not been brought to the point where specific benefit exists in a currently available form.

Claims 1, 3, 4, 6, 7, 28, 30, 31, 33, 34, 59, 72, 73, 75-77 and 91-106 are free of the prior art. At the time of filing the prior art did not teach or suggest a human/nonhuman primate chimeric embryo as claimed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is 703-308-1126. The examiner can normally be reached on M-Th, 8:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.



Deborah Crouch, Ph.D.
Primary Examiner
Art Unit 1632

September 10, 2003